REMARKS

Claims 1-13 and 15-24 are currently pending in this application. Claims 1-9 and 16-18 are withdrawn from consideration by the Examiner as allegedly being drawn to non-elected embodiments. Claim 14 was previously canceled without prejudice or disclaimer. Claims 10 and 13 are amended herein. Support for those amendments can be found throughout the specification, *e.g.*, at page 7, line 31; the table bridging lines 28-29 on page 12; the table bridging lines 12-13 on page 17; and the Examples 1-4 on pages 9-18. Thus, no new matter has been added.

FORMAL MATTERS

The Advisory Action dated April 25, 2008, indicates that the Amendment After Final filed March 14, 2008, was not entered. Applicant hereby withdraws the Amendment After Final dated March 14, 2008, in favor of the instant Amendment and Response Under 37 C.F.R. § 1.114.

REJECTION UNDER 35 U.S.C. § 112 - ENABLEMENT

In the Final Office Action dated November 16, 2007, the Office maintains the rejection of claims 10-13, 15, and 19-24 under 35 U.S.C. § 112 ¶ 1 as allegedly failing to comply with the enablement requirement. (Office Action at pp. 2-6.) Specifically, the Office cites Heimburger V. N. et al., "Factor VIII Concentrate, Highly-Purified and Heated in Solution," Drug Res., 31:619-622 (1981) ("*Heimburger*") as allegedly demonstrating the unpredictability of the claimed invention. *Id.* Applicant respectfully traverses.

"There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is 'undue.' These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure." M.P.E.P. § 2164.01(a), 8th Edition, August 2007 Revision (citing *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988)). The Office analyzes each of these factors and concludes that the instant invention requires "undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented." (Office Action at p. 4.) Applicant respectfully disagrees.

As the Office acknowledges, the nature of the invention (*Wands* Factor B) is a method for producing a concentrate of a Factor VIII:C-containing von Willebrand factor (vWF/FVIII:C), comprising fractional precipitation using an alkali metal salt and an amino acid chosen from glycine, α- or β-alanine, α-, β-, or γ-aminobutyric acid, lysine, valine, asparagine, and glutamic acid, wherein the concentrate has an increased content of high molecular weight multimers of vWF, and a ratio of von Willebrand factor ristocetin cofactor activity (vWF:RCoF) to von Willebrand factor antigen (vWF:Ag) of greater than 1. (*See* Office Action at pp. 2-3.) The Office also agrees that the level of skill in the art (*Wands* Factor D) is high. (*See* Office Action at p. 4.)

However, the Office contends that the previously presented claims are broad (*Wands* Factor A) "because they refer to a process for producing a concentrate of factor VIII:C-containing von Wilebrand factor (vWF/FVIII:C) wherein the concentrate has a

ratio of vWF:RcoF [sic] to vWFAg of greater than 1." (Office Action at p. 3.) Applicant respectfully disagrees that the claims are broad and submits that the Office has merely analyzed one element of the previously presented claims. The Office has failed to consider that the claims are also limited to: (1) alkali metal salts or alkaline earth metal salts; (2) amino acids chosen from glycine, α- or β-alanine, α-, β-, or γ-aminobutyric acid, lysine, valine, asparagine, and glutamic acid; and (3) concentrates having an increased content of high molecular weight multimers of vWF. In addition, the currently amended claims are limited to fractional precipitation methods using an effective amount of the precipitation reagents such that the resulting concentrates have the recited desired properties. Accordingly, Applicant respectfully submits that the scope of the claims is not overly broad.

The Office also contends that the amount of direction provided by the inventor (*Wands* Factor F) and the existence of working examples (*Wands* Factor G) are limited to "working examples 1 and 2 and Table 1 on pages 10 and 11" of the specification. (Office Action at p. 4.) Applicant respectfully disagrees and submits that the Office has failed to consider the teachings of Examples 3-5 and Tables 3, 4, 6, 8, and 9 on pages 14-21 of the specification. These Examples and Tables disclose additional methods according to the invention in which the resulting concentrate has a vWF:RCoF/vWF:Ag ratio greater than 1. In total, the specification provides **ten** examples of operative embodiments of the invention. Moreover, Examples 3-5 and Tables 4, 6, 8, and 9 also disclose methods in which the vWF:RCoF/vWF:Ag ratio is less than 1. By comparing the operable and inoperable examples disclosed in the specification, one skilled in the art can readily ascertain the effective conditions that produce a concentrate with a

vWF:RCoF/vWF:Ag ratio greater than 1. Accordingly, Applicant respectfully submits that the specification provides sufficient working examples and direction to allow one skilled in the art to practice the instantly claimed invention.

The Office's main argument focuses on the state of the prior art (*Wands* Factor C), the level of predictability in the art (*Wands* Factor E), and the quantity of experimentation needed to make or use the invention (*Wands* Factor H). Specifically, the Office contends that *Heimburger* establishes the state of the prior art and demonstrates that "the instant invention is unpredictable because the instant method claimed does not produce a concentrate in which the ratio of ristocetin to vWF is greater than 1 because the prior art reference teaches that the same method steps produce a concentrate in which the ratio is less than 1." (Office Action at p. 3.) In addition, the Office contends that "there is a large quantity of experimentation necessary to determine whether the method claimed, i.e. a process for producing a concentrate of a vWF/FVIII:C where the concentrate has a ratio of vWF:RcoF to vWF:Ag that is greater than 1, is actually claimed since the prior art by Heimburger et al. clearly teaches the same method that utilizes the same steps where the ratio for the same compositions is less than 1." (*Id.*) Applicant respectfully disagrees.

As discussed in the Declaration of Gerhardt Kumpe Under 37 C.F.R. § 1.132 ("*Kumpe Declaration*"), one of the inventive features of the instant application is the unexpected discovery that the concentration of amino acid used in the fractional precipitation affects whether the Factor VIII:C-containing von Willebrand factor concentrate produced exhibits a vWF:RCoF/vWF:Ag ratio is greater than 1. (*Kumpe Declaration* at ¶ 9.) Examples 1-4 on pages 9-18 of the specification demonstrate that

in all but one case, final concentrations of amino acid in excess of 110 g/l produced vWF:RCoF/vWF:Ag ratios less than 1, whereas ratios greater than 1 were consistently observed when the final concentration of amino acid did not exceed 110 g/l. (*See* Exhibit A.) Thus, Applicant has discovered that it is possible to reproducibly generate vWF/FVIII:C concentrates having vWF:RCoF/vWF:Ag ratios greater than 1 using an "effective amount" of amino acid such that the final concentration in the fractional precipitation does not exceed 110 g/l. Without acquiescing to the rejection and solely to facilitate prosecution, claims 10 and 13 are amended herein to recite that inventive feature.

The *Kumpe Declaration* also establishes that the final concentration of amino acid in *Heimburger* is 128.3 g/l. (*Id.* at ¶ 8.) Thus, the concentration of amino acid used in *Heimburger* exceeds 110 g/l, and the resulting vWF:RCoF/vWF:Ag ratio observed in that reference is less than 1. Since *Heimburger* does not use an "effective amount" of amino acid such that the vWF:RCoF/vWF:Ag ratio of the concentrate is greater than 1, the steps of the instant invention are not the same as *Heimburger*. Thus, the Office's argument that "since the steps are the same, the results must inherently be the same" (Office Action at page 6), does not apply to the currently amended claims. In fact, rather than calling the operability of the instant invention into question, *Heimburger* supports Applicant's discovery that an effective amount of amino acid must be used in the fractional precipitation to produce a Factor VIII:C-containing von Willebrand factor concentrate with a vWF:RCoF/vWF:Ag ratio is greater than 1.

For at least these reasons, Applicant respectfully submits that the instantly claimed invention is fully enabled by the originally filed specification. Accordingly,

Applicant respectfully requests that the rejection of claims 10-13, 15, and 19-24 under 35 U.S.C. § 112 ¶ 1 be withdrawn.

PRELIMINARY REJECTIONS UNDER 35 U.S.C. § 112

A. New Matter

The Advisory Action dated April 25, 2008, alleges that the phrase "less than or equal to 110 g/l" in the previously presented version of amended claim 10 would be rejected as introducing new matter, "since no support for such phrase or the claimed numerical value is presented in the specification." (Advisory Action at p. 2.) Applicant respectfully traverses. Without acquiescing to the preliminary rejection, and solely to facilitate prosecution, Applicant has removed the phrase "less than or equal to 110 g/l" from the currently pending claims. Instead, the currently pending claims recite the phrases "an effective amount" and "from about 67 to about 110 g/l." Applicant respectfully submits that the specification fully supports the currently pending claims.

To satisfy the written description requirement, a patent specification need only describe the claimed invention "in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." M.P.E.P. § 2163(I). Moreover, the subject matter of the claim need not be described literally in order for the disclosure to satisfy the written description requirement. M.P.E.P. § 2163.02. Even if every nuance of the claims is not explicitly described in the specification, the written description requirement can still be met. *See, e.g., Vas-Cath*, 935 F.2d 1555, 1563 (Fed. Cir. 1991); and *Martin v. Johnson*, 454 F.2d 746, 751 (C.C.P.A. 1972) (stating "the description need not be in ipsis verbis [*i.e.*, "in the same words"] to be sufficient").

Although the specification does not expressly recite the phrase "effective amount," the specification teaches that the concentration of amino acid used in the fractional precipitation affects whether the vWF/FVIII:C concentrate produced will exhibit a vWF:RCoF/vWF:Ag ratio greater than 1. Specifically the specification provides **ten** examples demonstrating that vWF:RCoF/vWF:Ag ratios greater than 1 were consistently observed when the final concentration of amino acid did not exceed 110 g/l. The specification also provides numerous examples showing that final concentrations of amino acid in excess of 110 g/l produced vWF:RCoF/vWF:Ag ratios less than 1. (*See also* Exhibit A.) By comparing the operable and inoperable examples disclosed in the specification, one skilled in the art can readily ascertain the "effective conditions" that produce a vWF/FVIII:C concentrate with a vWF:RCoF/vWF:Ag ratio greater than 1. Thus, one skilled in the art would reasonably conclude that Applicant was in possession of an "effective amount" of amino acid for producing vWF/FVIII:C concentrates with vWF:RCoF/vWF:Ag ratios greater than 1, as recited in currently amended claim 10.

Likewise, although the specification does not expressly recite a range "from about 67 to about 110 g/l" amino acid, the specification recites the range of final concentrations of amino acid "from 70 to 160 g/l," and also discloses exemplary precipitations in which the final concentration of amino acid is 66.7 g/l and 109.6 g/l. *See* specification at p. 7, ln. 31; p. 12, 2nd table, Batch C; and p. 17, 1st table, Batch 2. One skilled in the art would understand that the decimal numbers 66.7 and 109.6 g/l, round to the whole numbers, 67 and 110 g/l, respectively, and thus, would recognize that 66.7 and 109.6 g/l are <u>about</u> 67 and 110 g/l, respectively. Moreover, there is no requirement for the specification to provide literal support for the word "about" recited in

the claims, if one skilled in the art would recognize from the specification that the claimed values were intended to be approximate. *Eiselstein v. Frank*, 52 F.3d 1035, 1039 (Fed Cir 1995). In *Eiselstein*, the court found that recitation of both inexact ranges and precise values accurate to one-hundredth of a percent in the specification "indicates that Eiselstein knew how to be precise when he intended to, and supports the conclusion that otherwise, when a whole number was stated, a precise amount was not intended." *Id.* Here, as in *Eiselstein*, the specification recites a combination of inexact values and more precise values, indicating that when a whole number is stated in the claims, a precise amount is not intended. *See, e.g.*, p. 7, ln. 31 ("70 to 160 g/l glycine"); and pp. 12 and 17 (teaching glycine concentrations of 66.7 g/l, 71.1 g/l, 90.4 g/l, 109.6 g/l, 128.3 g/l, and 160.0 g/l). Thus, the instant specification provides sufficient support for the word "about" in claim 13.

In addition, there is no requirement that the specification provide literal support for a claimed range, if the range recited in the claim is based on the examples disclosed in the specification. *Ex parte Jackson*, 110 U.S.P.Q. 561 (BPAI 1956). In *Jackson*, the claims recited ranges that had been compiled from the individual values presented in the examples. The Board held that "since the Office places much emphasis on the disclosure of the examples which are present in the specification, it is ordinarily not improper to use all of the examples to set up a range of established operativeness." *Id.* Here, as in *Jackson*, Applicant has used the values presented in the examples to establish a range of operable values in claim 13. Specifically, Applicant has used the values of about 67 g/l and abut 110 g/l presented in Examples 2 and 4 to more particularly point out and distinctly claim the lower end and limit the upper end of the

range to read on operable embodiments of the claimed invention. Thus, one skilled in the art would reasonably conclude that Applicant was in possession of a range of amino acid concentrations "from about 67 to about 110 g/l," as recited in claim 13.

For at least these reasons, Applicant submits that the currently pending claims are fully supported by the originally-filed specification.

B. Indefiniteness

The Advisory Action dated April 25, 2008, alleges that the phrase "less than or equal to 110 g/l" in the previously presented version of amended claim 10 would be rejected for indefiniteness, "since the numerical values claimed are 'less than 110 g/l' thus could be represented by a value of zero i.e. '0 g/l', which is less than 110 g/l, for example." (Advisory Action at p. 2.) Applicant respectfully traverses. Without acquiescing to the preliminary rejection, and solely to facilitate prosecution, Applicant has removed the phrase "less than or equal to 110 g/l" from the currently pending claims. Instead, the currently pending claims recite the phrases "an effective amount" and "from about 67 to about 110 g/l." Applicant respectfully submits that the currently amended claims are definite.

The proper test for indefiniteness of claims reciting the phrase "effective amount" "is whether or not one skilled in the art could determine specific values for the amount based on the disclosure." M.P.E.P. § 2173.05(c) (citing *In re Mattison*, 509 F.2d 563 (CCPA 1975)). Here, as discussed above, the specification provides **ten** examples of operative embodiments of the invention in which the fractional precipitations produced a vWF:RCoF/vWF:Ag ratio greater than 1, and also discloses methods in which the vWF:RCoF/vWF:Ag ratio is less than 1. By comparing the operable and inoperable

examples disclosed in the specification, one skilled in the art can readily ascertain the "effective conditions" that produce a concentrate with a vWF:RCoF/vWF:Ag ratio greater than 1. Accordingly, Applicant respectfully submits that based on the teachings of the specification, the currently pending claims are definite because one skilled in the art could readily determine the range of values encompassed by the phrase "an effective amount" in claim 1.

In determining the definiteness of the range encompassed by the term "about" in a claim, "one must consider the context of the term as it is used in the specification and claims of the application." M.P.E.P. § 2173.05(b) (citing *Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd.,* 476 F.3d 1321, 1326 (Fed. Cir. 2007)). Here, as discussed above, the specification clearly indicates that the instant invention comprises a range of operable amino acid concentrations. (*See e.g.*, specification at p. 22, ll. 24-28 ("It was evident from this that a partitioning of the vWF multimers according to size can be achieved by appropriate adjustment of the equilibrium with NaCl and glycine also in the culture supernatant which may contain both recombinant FVIII:C and plasma vWF.") (emphasis added)). In particular, the specification recites a range of whole number values comprising "70 to 160 g/l glycine," and also exemplifies the specific decimal values 66.7 g/l, 71.1 g/l, 90.4 g/l, 109.6 g/l, 128.3 g/l, and 160.0 g/l glycine. (*See* specification at p. 7, ln. 31, and the tables on pages 12 and 17.) Thus, the specification indicates that when a whole number is stated in the claims, decimal values closely related to that whole number value are included. Accordingly, Applicant respectfully submits that based on the teachings of the specification, one skilled in the art could readily determine the range of values encompassed by the term "about" in claim 13.

For at least these reasons, Applicant submits that the phrases "an effective amount" and "from about 67 to about 110 g/l" in the currently amended claims are definite.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: July 14, 2008

By: Amanda K. Murphy
Amanda K. Murphy
Reg. No. 59,387

Attachments: Declaration of Gerhardt Kumpe Under 37 C.F.R. § 1.132 with Exhibit A.